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Review

Fetal neonatal hyperthyroidism: diagnostic and therapeutic approachment

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Abstract

Fetal and neonatal hyperthyroidism may occur in mothers with Graves' disease. Fetal thyrotoxicosis manifestation is observed with the transition of TSH receptor stimulating antibodies to the fetus from the 17th-20th weeks of pregnancy and with the fetal TSH receptors becoming responsive after 20 weeks. The diagnosis is confirmed by fetal tachycardia, goiter and bone age advancement in pregnancy and maternal treatment is conducted in accordance. The probability of neonatal hyperthyroidism is high in the babies of mothers that have ongoing antithyroid requirement and higher antibody levels in the last months of pregnancy. Clinical manifestation may be delayed by 7-17 days because of the antithyroid drugs taken by the mother. Neonatal hyperthyroidism symptoms can be confused with sepsis and congenital viral infections. Herein, the diagnosis and therapeutic approach are reviewed in cases of fetal neonatal hyperthyroidism. (Turk Pediatri Ars 2017; 52: 1-9)

Keywords: Fetal hyperthyroidism, Graves' disease, neonatal hyperthyroidism, pregnancy

Introduction

Fetal and neonatal hyperthyrodism related with maternal Graves' disease is not observed as frequently as congenital hypothyroidism. However, if it is not diagnosed early and treated correctly, it leads to a series of problems in the pregnant mother and creates somatic and developmental problems in the baby. Approximately 1% of childhood thyrotoxicoses occur in the neonatal period. Maternal Graves' disease is present in the majority of cases. In addition, a picture of permanent non-autoimmune hyperthyrodism occurs in the thyroid-stimulating hormone (TSH) receptor (TSHR) or GNAS gene activating mutations (1).

Graves' disease in pregnancy: Graves' disease is observed with a rate of 0.1-0.4% in pregnant women (2). It may be present before pregnancy or emerge during pregnancy. Antibody levels increase again in pregnancy in patients in whom thyroidectomy was performed and radioactive iodine treatment was administered years previously or in patients who were controlled with antithyroid drugs (3). It was observed that antibody levels increased in about 1.5 years in 20-30% of patients who underwent thyroidectomy or were given antithyroid medication, and in five years in 40% of the patients who received radioactive iodine (4). Use of thyroxine by the patients may hide the actual diagnosis. Hypertension related with pregnancy, congestive heart failure, thyroid crisis, infections, venous thrombosis, pulmonary thromboembolism, and placental separation are observed in the mother, and some of the signs and symptoms may be considered problems of pregnancy. Stillbirth, abortus, premature delivery, intrauterine growth retardation, malformations related with anti-thyroid drugs, neutropenia, goitre, and fetal hypothyroidism are observed in the fetus (2, 5, 6). The diagnosis of Graves' disease is made with measurement of FT3, FT4, TSH, and TSHR antibodies in pregnancy. The American Thyroid Association recommends that the cut-off value for TSH should be 0.1-2.5 mU/L in the first trimester, 0.2-3.0 mU/L in the second trimester, and 0.3-3.0 mU/L in the third trimester, and hyperthyroidism should be investigated when the TSH level is below 0.1 mU/L (7). The TSHR antibodies in the mother may have stimulatory or blocking activity or may be ineffective. Rarely, the stimulatory antibodies in the patient may be transformed into blocking antibodies or

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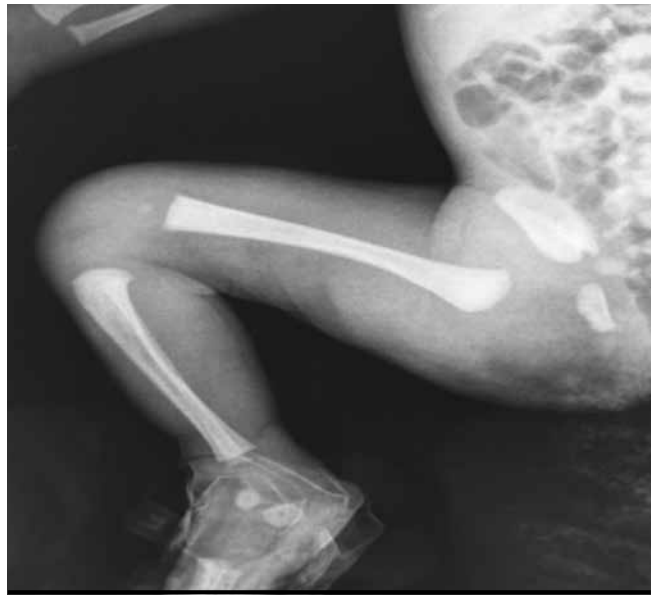
vice versa (8). Measurement of TSHR antibodies is initiated in the 20-24th gestational week because the fetal TSH receptors start to respond from the 20th week. A 3-5-fold increase in the stimulatory antibodies shows the risk of fetal hyperthyroidism (7).

Treatment approaches: The effects of propylthiouracil (PTU) and methimazole are similar in controlling thyrotoxicosis in pregnancy. Both drugs decrease synthesis of thyroid hormone by inhibiting the use of iodine in the thyroid gland and also inhibiting production of TSHR antibody through their immunosupressive effects. Reduction of transformation of peripheral T4 to T3 by PTU is a second advantage. Propylthiouracil is preferred initially, because methimazole causes a series of malformation when used in the first trimester. If necessary, beta-blockers may be used (2, 9).

Fetal adverse effects of antithyroid drugs: A significant portion of the adverse effects of antithyroid drugs used in pregnancy is constituted by teratogenic effects. Embryopathy related with methamizole in the first trimester occurs in 2-4/100 babies and includes aplasia cutis, cleft palate-lip, Down syndrome, choanal atresia, tracheo-esophageal fistula, hiatal hernia, tracheomalacia, hypertrophic pyloric stenosis, hypothelia, athelia, omphalocele, anomalies of the omphalomesenteric ductus, hearing deficit, atrial septal defect, ventricular septal defect, patent ductus arteriosus, pulmonary stenosis, imperforated anus, hypospadias, anencephaly, polydactilia, small ear, broad and dispersed eyebrows, and broad nasal root (9). A case of bilateral renal agenesis related with methamizole has been published (10). In addition, it has been reported that the possibility of obstructive uropathy is increased by 5-fold in relation with maternal hyperthyroidism independent of antithyroid drugs (11). Similary, developmental dysplasia of the hip has been observed more frequently in babies of mothers with hyperthyroidism (12). Although some malformations are observed with both drugs, it has been reported that preauricular fistula, cysts, and hydronephrosis may be observed in relation with PTU (13). Intrauterine growth is affected by beta-blockers and these drugs may lead to bradicardia and hypoglycemia in newborns (2).

Fetal hyperthyroidism: Thyroid-stimulating hormone receptor-stimulating antibodies, which occur and reach high levels in mothers who exhibit a picture of Graves' disease, cross the placenta and lead to a picture of fetal hyperthyroidism because they have a structure like immunoglobulin-G. Ten percent of the mother's level is transferred to the fetus in the 17-22th gestational week and 50% is transferred to the fetus in the 28th-32nd weeks. Subsequently, the level in the fetus gradually increases and exceeds the mother's level in the term newborn (14). Although it has been proposed that the clinical picture may start from the 21st week when the antibody level increases and the fetal TSH receptors become responsive, the picture of fetal hyperthyroidism generally becomes prominent in the 26-28th weeks (5). Both sexes are affected equally. Spontaneous abortus, fetal death, and intrauterine growth restriction are observed in fetuses of mothers who are not treated after the second half of pregnancy. The growth problem is related with both hyperthyroidism and preeclampsia. Other fetal findings include tachycardia (heart beat >160/min), heart failure, hydropsis, acceleration in bone age, craniosynocstosis, and microcephaly (15).

In the follow-up, fetal tachycardia (>160/min), advanced bone age, occurence of goitre, and increased blood supply found using Doppler ultrasonography are significant. Goitre may be related with hyperthyroidism or the dose of the antithyroid drug given to the mother. If hypothyroidism is present, the heart beat rate is found as 100/min. For the definition of goitre, a fetal neck circumference value above the 95th percentile described by Ranzini et al. (16) should be considered. If there is a large goitre, it may lead to hyperextension and polyhydramniosis. If the blood supply is more intense in the center, the possibility of hyperthyroidism is higher. If the blood supply is more intense in the periphery, the



Picture 1. Small distal femur epiphysis nucleus in the 31st-32nd gestational week (from Erciyes University, Medical Faculty, Divison of Neonatology Archive)

possibility of hypothyroidism is higher (17). The fetal bone age is interpreted with knee epiphysis nuclei. The distal femoral epiphysis becomes prominent as a point at about the 32nd week. Appearance of the distal femoral epiphyisis before the 31st gestational week is considered advanced bone age and absence of the distal femoral epiphysis at the 33rd week is considered delayed bone age (Picture 1) (18).

The TSHR antibody level is measured in maternal and fetal blood samples. After the diagnosis is made, antithyroid treatment is initiated in the mother and hyperthyroidism is generally controlled in 14 days. Anthyroid drugs should be given at low doses and such that the fetal heart rate is kept at 140/min. Considering that a series of malformations occur with use of methimazole in pregnancy, propylthiouracil should be preferred in the first trimester (19). Beta-blockers may be used in severe cases. However, one should be cautious because of adverse effects including intrauterine growth retardation, prolongation of labor, neonatal bradicardia, hypotension, hypoglycemia, and prolonged jaundice. Radioactive iodine treatment is not administered in pregnancy. Thyroidectomy may be performed in very special cases. Administration of iodine to mothers leads to neonatal goitre and hypothyroidism (2).

Neonatal Graves' disease: The prevalence of Graves' disease in pregnancy is about 0.1-0.2% and problems occur in only 1% of mothers with this condition (2, 3). However, this rate increases to 2-10% when biochemical hyperthyroidism without clinical reflections accompanies (3). Neonatal hyperthyroidism was found in 8% of babies of 108 mothers with Graves' disease, 71 of whom were in remission and 36 were receiving antithyroid treatment, but a severe clinical picture was observed in 5% of the babies (20). Mortimer et al. (21) found the picture of hyperthyroidism with a rate of 8% in babies born from 48 mothers with Graves' disease, 44 of whom were in an active state. Mitsuda et al. (22) followed up 230 pregnant women with Graves' disease and found clinical and biochemical hyperthyroidism with a rate of 5.6%, and transient hypothyroidism with a rate of 10.7%. In another study, the babies of 86 mothers with Graves' disease were followed up and marked hyperthyroidism was found with a rate of 4%, whereas the FT4 level was found above the 95th percentile on the fifth day in 92.9% of the babies (subclinical form). The FT4 level returned to normal on the 15th day in babies with the subclinical form and TSH supression continued for a further three months (23).

Pathogenesis: It is known that the TSH receptor-stimulating antibodies, which are produced in the mother, cross the placenta and lead to fetal and neonatal hyperthyroidism (23). In addition, thyroid hormones transferred from mothers who are not being treated may also cause a similar picture. The antibodies decrease towards the end of pregnancy, but fetal thyrotoxicosis becomes severe in cases where levels remain high and the possibility of neonatal thyrotoxicosis increases. Thyroid-stimulating hormone receptor antibody produced in the mother may be stimulating or blocking. The clinical picture occurs as hypo- or hyperthyroidism according to the type of the TSHR antibody. If the TSHR stimulating and blocking antibodies are in balance in fetal life, the newborn may be initially euthyroid. Late neonatal hyperthyroidism may occur in the late period in relation with the antibodies remaining in the serum because the half-life of the blocking antibodies is about 12 days (24). Although this picture is observed in three weeks at the earliest, it generally occurs in 6-8 weeks in the postnatal period (15, 19).

Clinical picture: The picture of thyrotoxicosis in the newborn varies according to the antithyroid drugs used by the mother and the level of blocking antibodies. It may be observed immediately after delivery in babies of untreated mothers. Among the drugs used by the mother, PTC maintains its activity for 12-24 hours in the baby. This time period is 36-72 hours for methimazole (25). The clinical signs and symptoms may be delayed up to 7-10 days because of antithyroid drugs or

Picture 2. Vivacious look and exophthalmos in a hyperthyroidic baby (from Erciyes University, Medical Faculty, Divison of Neonatology Archive)With permission of Daniëlle C.M. van der Kaay

TSHR blocking antibodies found in the serum (26). In another study, it was observed that the clinical picture appeared in the postnatal 1st-3rd days in babies of mothers who were not using medication, and in the postnatal 7th-17th days in the other babies (27). The clinical picture may not always be prominent. Vivacious look and exophthalmos may be the first findings to be noted (Picture 2). The general signs and symptoms include intrauterine growth retardation, exaggerated Moro reflex, increase in the other reflexes, craniosynostosis, microcephaly, frontal bossing, triangular face, periorbital edema, goitre, excessive restlessness, hyperactivity, irritability, sleep disorder, inability to gain weight despite excessive appetite, reduction in the subcutaneous adipose tissue, diarrhea, vomiting, fever, sweating, tachypnea, arrythmia, supraventricular tachycardia, systolic hypertension, hypertensive encephalopathy, heart failure, pulmonary hypertension, chilothorax, cholestasis, increase in the levels of AST, ALT and direct bilirubin, hypoglycemia, thrombocytopenia, hyperviscosity, hepatosplenomegaly, lymphadenopathy, hip dysplasia, prolonged acrocyanosis, and sialadenitis (4, 18). Radiography reveals an enlarged thymus and advanced bone age. Goitre is found in 50% of cases, but not so large as to cause airway obstruction. Palpebral retraction is related with thyrotoxicosis and exophthalmos is related with autoimmune pathology. The clinical picture resolves in 3-16 weeks with elimination of maternal antibodies (15). It has been reported that biochemical hypothyrodism is observed in both twins initially, whereas hyperthyroidism may be observed in one and biochemical hypothyroidism may be observed in the other subsequently (28).

Predictor markers for neonatal hyperthyroidism: A maternal TSHR-stimulating antibody level of 350-500% (n<125%) and a TBII level of >40-70% (n<10-15%) indicates that thyrotoxicosis may be present in the newborn (29). A TSHR-stimulating level higher than three-fold the upper limit of normal in the postnatal 1st-7th days is predictive for neonatal hyperthyroidism (6).

Diagnosis: Neonatal hyperthyroidism should be evaluated in cases where TSHR antibodies are high in pregnancy, a picture of thyrotoxicosis requiring antithyroid treatment is present in the 3rd trimester, fetal-neonatal hyperthyroidism developed in previous pregnancies, fetal goitre, tahycardia and intrauterine growth retardation or familial TSHR-activated mutation is found. FT3-FT4-TSH should be measured initially, but the tests should be repeated 3-7 days later if the mother is using antithyroid drugs, and the levels should be interpreted according to normal values of the neonatal period. In cases where increased TSHR antibody levels were found in the third trimester, the chord blood antibiody level was found increased in 73% of babies (30). The chord blood TSHR antibody is predictive, whereas chord blood FT4 levels have been reported as having low predictability (19, 22).

Differential diagnosis: Hyperthyroidism may be confused with congential viral infection, neonatal sepsis, congenital heart diseases, and tachyarrythmia. The picture of tremor, sweating, sneeze, vivacious reflexes, and fever observed in babies with narcotic withdrawal syndrome may raise a suspicion of hyperthyroidism (31). A diagnosis of infantile colic may be made in cases of late-onset hyperthyroidism. Prominent eyes may be observed in a series of syndromes outside hyperthyroidism, but the clinical picture of hyperthyroidism is absent in these cases.

Treatment: Although it is mostly regarded as a transient problem, early and appropriate treatment is significant because of heart failure in the acute phase, and morbidities including craniosynostosis, microcephaly, and mental retardation in the long term. The mainstay of treatment is administration of antithyroid drug. Antithyroid drugs decrease thyroid hormone synthesis by inhibiting thyroid peroxidase. Propylthiouracil inhibits thyroid hormone synthesis and peripheral transformation of T4 to T3 and is given orally three times a day at a dose of 0.2-0.5 mg/kg/day. Methimazole is used in two doses according to the severity of the clinical picture (32). Use of methimazole is recommended because of the hepatotoxic effects of PTC. Transient leukopneia, increased liver enzymes and skin eruption may be observed with use of methimazole. Rarely, more severe agranulocytosis, hepatotoxicity, vasculitis, and Stevens-Johnson syndrome may be observed (33). Suppressive action occurs in 1-2 weeks. In preterm babies, reduction in hormone levels may occur more rapidly because of high susceptibility to drugs and insufficient depot (9). In severe cases, saturated potassium iodide solution (SSKI) (1 drop/day) or Lugol solution (1-3 drops/day) is added to treatment to prevent the thyroid hormones synthesized before from entering the circulation. However, these solutions should not be used for long periods because of iodine escape phenomenon and the disappearance of action after a while. Lugol and SSKI should be given at least 1 hour after the methimazole dose. The rationale for this is preventing uptake

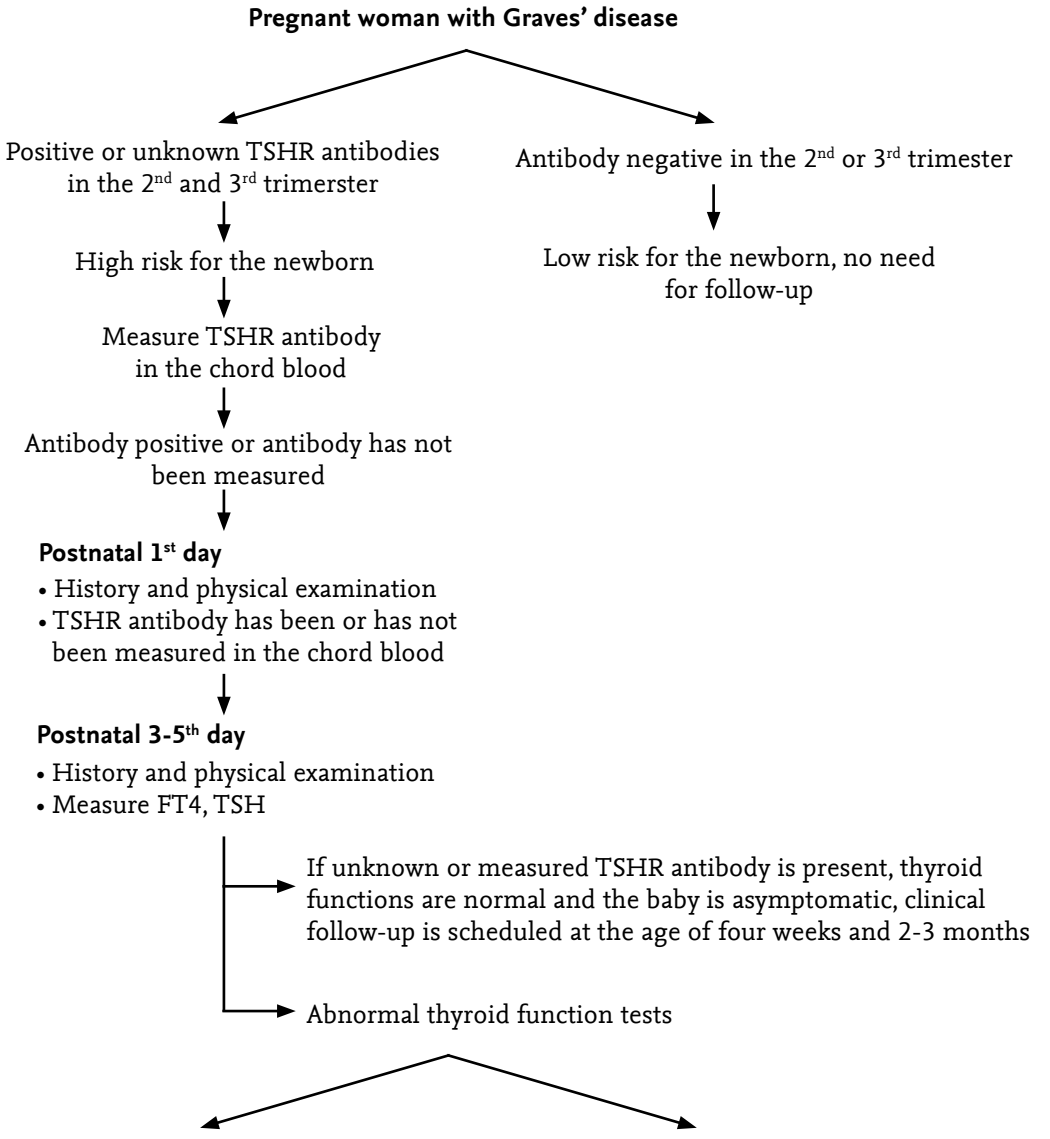


Figure 1. Postnatal follow-up algorithm in the babies of mothers with Graves' disease
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and use of iodine by the thyroid gland for synthesis of new hormone (31). Sodium iopanoate (iopanoic acid) (500 mg orally every three days) or glucocorticoids (prednisolone in 1-2 doses at a dose of 2 mg/kg/day) may be used in severe cases to prevent thyroid hormone production and peripheral transformation of T4 to T3 (32). Propranolol, which is a beta-blocker, is used at a dose of 2 mg/kg/day to decrease the cardiac rate and peripheral transformation of T4 to T3 (5, 19, 32).

A suppression and replacement treatment protocol may also be used in these patients (9). In this method, antithyroid drug is given at a constant dose and thyroxine is added when the FT4 level reduces to the hypothyroidism range. Initially, the follow-up visits are scheduled once a week. The dose of antithyroid drug is reduced when the FT3 and FT4 levels reduce to the lower half of the normal rage for age and treatment is discontinued when the TSHR antibody becomes negative in order to decrease the risk of relapse. The TSH level may remain suppressed for a while after euthyroidism is provided. IVIG treatment may be recommended in very severe cases. Hence, a rapid improvement was obvserved in thyroid hormone levels in five days when IVIG was given at a dose of 1 g on the 1st and 4th days in a baby aged 8 days who had severe thyrotoxicosis (34). Another treatment method is blood exchange and subsequent use of Lugol (35). The thyroxine level decreases by 50% with blood exchange. The half-life of the antibodies transferred from the mother is approximately 12 days. Treatment is continued as long as the TSHR antibodies are positive. The treatment period ranges between 3 and 12 weeks (mean: 1-2 months). Treatment in some cases is summarized in Figure 1 (32).

Prognosis: The prognosis depends on the time of the fetal-neonatal process and the severity of the clinical picture. In one study, the thyroid volume, thyroid functions, somatic and psychomotor development at the age of 7-8 years were not found different in babies of normal mothers and mothers with Graves' disease (36). Neuropsychiatric sequela, which were observed in some patients, are thought to be related with prematurity rather than the morbidity.

Lactation: Theoretically, it is recommended that methimazole should be preferred in nursing mothers. The American Academy of Pediatrics and Endocrine Association recommends a maximum dose of 300 mg/day for PTU and 20 mg/day for methimazole (7). It has been emphasized that the drugs should be given in the fractionated form immediately after nursing or ideally 3-4 hours before the next nursing. Another significant point is the fact that the TSHR antibodies (life in the circulation: 2 months) may be transferred to the baby by way of breastmilk and cause neonatal hyperthyroidism, which requires treatment even if the mother is euthyroid (37).

Other causes of neonatal thyrotoxicosis

1. **Use of high-dose thyroxine:** In the treatment of congenital hypothyroidism, an appropriate dose of thyroxine is initiated according to the severity of the disease and the FT4-TSH levels are measured 1-2 weeks later. The serum FT4 level is maintained in the upper half of the normal range and TSH should be maintained in the normal range. It the TSH level is <0.05 mU/L, the dose is high (38). In cases of overdose, excessive appetite, inability to gain weight, restlessness, sleeplessness, sweating, frequent defecation, and tachycardia are found. Craniosynostosis may develop if the follow-up is not pursued appropriately.

2. **Iodine-induced hyperthyroidism:** Iodine overload in pregnancy and in the neonatal period usually leads to hypothyroidism (39). On the other hand, it may rarely lead to hyperthyroidism. Thyrotoxicosis following mediastinal lavage with an iodine-containing antiseptic substance that resolved approximately in one month was reported in a 22-day-old patient (40).

3. **Autosomal dominant non-autoimmune hyperthyroidism:** This condition was defined in 1994 for the first time and occurs as a result of activated mutation in the TSH receptor gene (41). Toxic thyroid hyperplasia occuring at various ages in at least two generations, absence of thyroid antibodies, lack of ophthalmopathy-dermopathy and autosomal dominant inheritance suggest this condition (42). In addition, it may be related with sporadic germline mutations. Late-onset and mild hyperthyroidism is generally observed in hereditary TSHR-activated mutations, whereas severe neonatal thyrotoxicosis is observed in sporadic cases, though this is not a definite rule (42). Different clinical pictures in individuals with the same mutation suggest that environmental factors and genetic-epigenetic mechanisms are also involved. In the presence of somatic-activated mutation (serin281-isoleucin) in the extracellular TSH-binding point of the TSH re-

ceptor, toxic adenoma may develop and cause congenital hyperthyroidism (43).

Antithyroid drugs are used primarily in the treatment. However, partial or total thyroidectomy is performed in patients who cannot be controlled with medical treatment and whose initial goitre gains multinodular character in time or radioactive iodine treatment may be planned in older children (41).

4. **McCune-Albright syndrome:** In McCune-Albright syndrome, an activated mutation is present in the GNAS gene, which encodes the alpha-subunit of G proteins, and hyperfunction is observed in endocrine glands (1). A case of neonatal hyperthyroidism associated with Cushing syndrome was published (44). In this case, the diagnosis was made with polyostotic fibrous dysplasia and hyperpigmentation and the patient died of heart failure at the age of four despite antithyroid treatment. Postmortem examination revealed ovarian cysts and multinodular hyperplasia in the thyroid and adrenal glands (45).

5. **Thyroid Receptor Beta Gene Mutation (M313T):** It was reported that PTU treatment was initiated for treatment of thyrotoxicosis when the FT4 level was increased and TSH was normal in a baby whose body weight did not increase in the neonatal period; the FT4 level was reduced to the normal level, but THS increased 27 days later. A thyroid receptor beta gene mutation (M313T) was found in the mother of this baby during investigations performed because of thyrotoxicosis and secondary infertility (46). It should be kept in mind that a picture of thyrotoxicosis may be observed in the neonatal period in such cases.

6. **Use of biotin:** In babies who receive biotin treatment, the FT3 and FT4 levels are increased and TSH level is suppressed because of interference. This condition is named biochemical neonatal hyperthyroidism and a clinical picture is absent in these patients (47).

Maternal Graves' and fetal-neonatal hypothyroidism: Fetal hypothyroidism may occur in the presence of blocking maternal TSHR antibodies and when the maternal TSHR antibodies are transformed into the blocking type or when high-dose antithyroid drug is given to the mother. Other problems found in the babies of mothers with Graves' disease include transient central hypothyroidism, primary hypothyroidism, and isolated hyperthyrotropinemia (28, 30, 48-50). This condition may be observed in the early postnatal period, following a short-term picture of hyperthyroidism or euthyroidism, or the picture of hypothyroidism may be observed before the stage of hyperthyroidism (8, 30). Thyroid-stimulating hormone was found increased with a rate of 14-21% and FT4 was found decreased with a rate of 6-7% in the chord blood of babies whose mothers used antithyroid drugs (48). Neonatal central hypothyroidism may develop in the baby following fetal hyperthyroidism related with insufficent treatment of the mother for Graves' disease. When 18 babies who were found to have such central hypothyroidism were analyzed, it was reported that the diagnosis was made on the 4^{th}-7^{th} days in T4-based hypothyroidism screening in 11 patients, transient hyperthyroidism was observed before hypothyroidism in one baby, and the other six babies were euthyroid in the first month before developing central hypothyroidism (49). It is thought that increased T4 levels reaching the fetus because of maternal hyperthyroidism causes problems in maturation or regulation of the fetal hypothalamo-pituitary-thyroid axis or thyroid receptor antibodies lead to supression in TSH production by binding to the TSH receptors in the pituitary gland (45, 46). In some of these babies, a picture of transient primary hypothyroidism may occur before the picture of hyperthyroidism develops (48). Thyroid-stimulating hormone was found increased with a rate of 14-21% and FT4 was found decreased with a rate of 6-7% in the chord blood of babies whose mothers used antithyroid drugs (48). In other studies, a transient increase in TSH was found with a rate of 7.8% and transient primary hypothyroidism was found with a rate of 2-9% (22). Primary hypothyroidism may sometimes be caused by high doses of antithyroid drugs. It has been proposed that primary hypothyroidism may occur with transformation of the TSHR-stimulating antibodies into blocking antibodies independent of the drug dose in some cases (8).

Babies who are found to have primary hypothyroidism were evaluated clinically and L-T4 treatment was initiated. After a few months of L-T4 treatment, serum T4 levels returned to normal and a normal reponse to TRH stimulus was obtained. Elimination of the picture of hypothyroidism may last 3-19 months (32).

In conclusion, maternal Graves' disease affects the fetal, neonatal, and childhood periods. The therapeutic

approach includes normalization of maternal thyroid functions. Babies should be followed up by a multidisciplinary team consisting of adult endocrinology, perinatology, neonatology, pediatric endocrinology, and pediatric radiology in terms of potential risk factors.

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